FORM PTO-1390 REV. 2/01T — U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37CFR1.5)
07579 0016	10/070361

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU00/01056	September 6, 2000	September 6, 1999

TITLE OF INVENTION
COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

APPLICANT(S) FOR DO/EO/US
Andrew HEATON; Naresh KUMAR; Graham Edmund KELLY; and Alan HUSBAND

Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☒ is attached hereto (required only if not communicated by the International Bureau.
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ Information Disclosure Statement under 37 CFR 1.97 and 1.98
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
   a. ☒ Copy of cover page of International Publication No. WO01/17986 A1
   b. ☐ Copy of Notification of Missing Requirements.
   c. ☐

U.S. APPLICATION NO (If known, see 37CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/070361	PCT/AU00/01056	07579 0016

21. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1 482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTOand all claims satisfied provisions of PCT Article 33 (1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1040.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total Claims	16	- 20 =	0	x $18.00	$	
Independent Claims	2	-3 =	0	x $84 00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$280 00	$280.00	
TOTAL OF THE ABOVE CALCULATIONS =					$1320.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.					$660.00	
SUBTOTAL =					$660.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest priority date (37 CFR 1.492(f)).					$	
TOTAL NATIONAL FEE =					660 00	
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +					$	
TOTAL FEES ENCLOSED =					$660.00	
					Amount to be refunded:	$
					charged:	$

a. ☒ A check in the amount of $ 660.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

DATED: March 5, 2002

SIGNATURE

Ernest F. Chapman, Reg. No. 25,961

NAME/REGISTRATION NO.

PATENT
Attorney Docket No. 07579.0016
CUSTOMER NUMBER 22,852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. national phase of PCT/AU00/01056

Inventors: Andrew HEATON et al.

Serial No.: Not Yet Assigned

Filed: March 5, 2002

For: COMPOSITIONS AND THERAPEUTIC METHODS INVOLOVING ISOFLAVONES AND ANALOGUES THEREOF

Group Art Unit:

Examiner:

Assistant Commissioner for Patents
Washington, DC 20231

BOX: PCT

Sir:

PRELIMINARY AMENDMENT

Prior to examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel without prejudice or disclaimer now pending claims 1-11 and replace them with the following complete set of claims 12-22:

12. (New) An isoflavone compound or analogue thereof of the general formula I:

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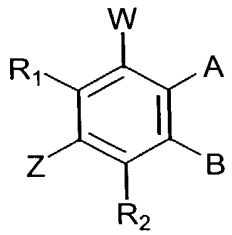


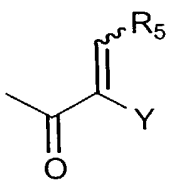
(I)

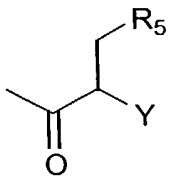
in which

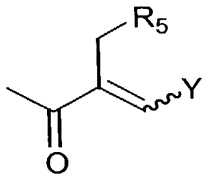
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

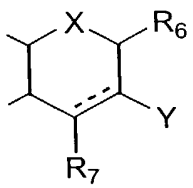


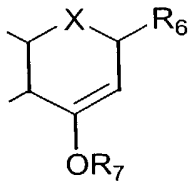


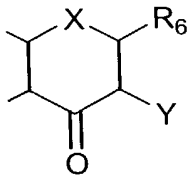


, or

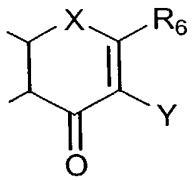
W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

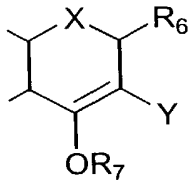






, or





W, A and B taken together with the groups to which they are associated comprise

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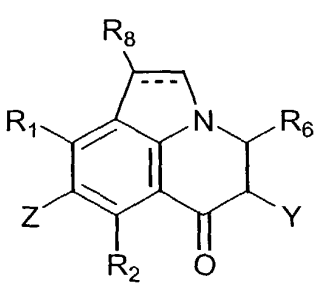
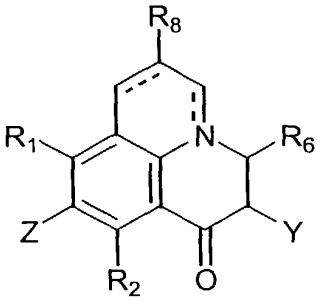
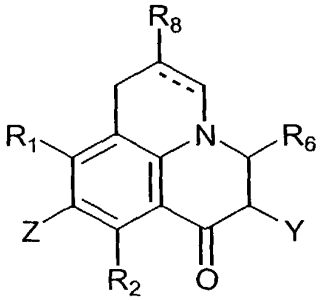
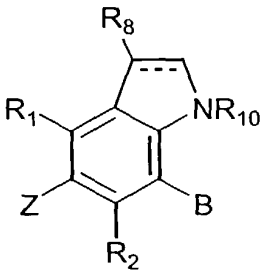
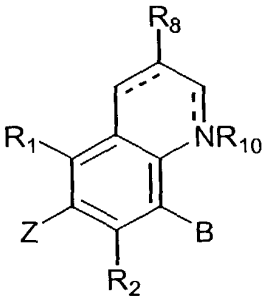
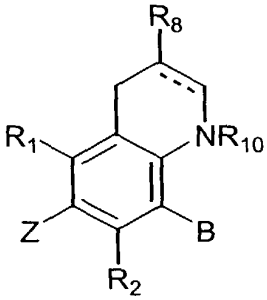
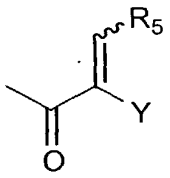
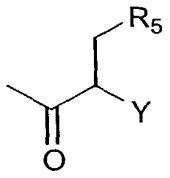
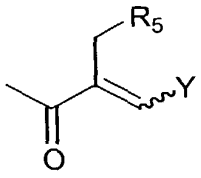



, or

W and A taken together with the groups to which they are associated comprise

and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

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R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

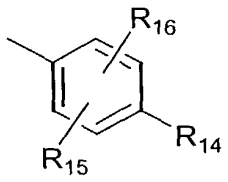
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the symbol "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not phenyl, 4-hydroxyphenyl, 4-alkoxyphenyl or 4-alkylphenyl;

when

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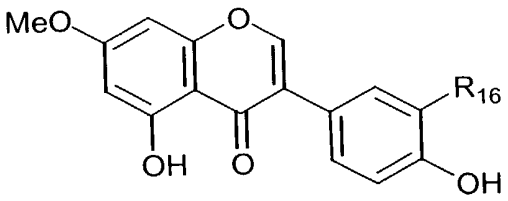
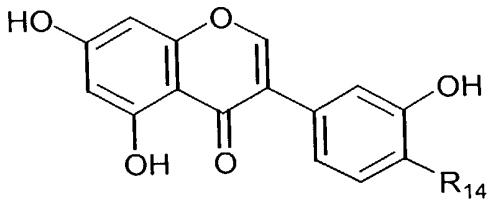
R_1 and R_2 are hydroxy, and
R_6 and W are hydrogen, then
Y is not phenyl; and

when
R_1 is hydroxy, and
R_2, R_6 and W are hydrogen, then
Y is not 4'-hydroxy-3'-methoxyphenyl; and

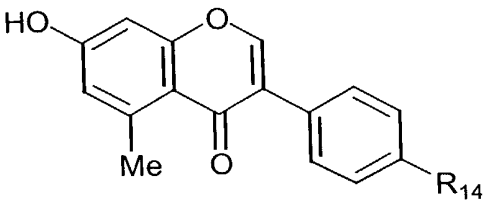
with the proviso that the following compounds are excluded:



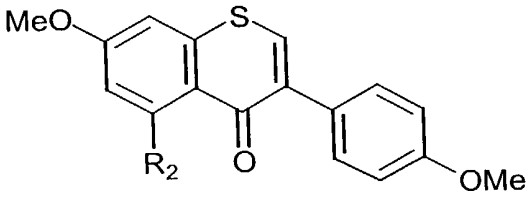
R_{16} = H, OH



R_{14} = OH, OMe



R_{14} = Me, Cl



R_2 = H, OMe

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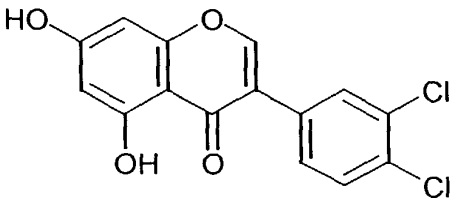
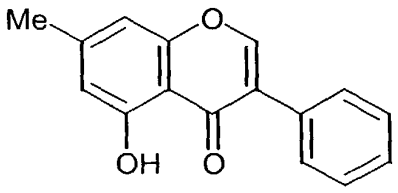
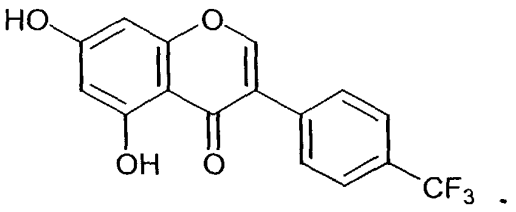
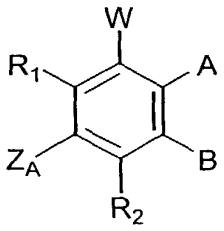






13. (New) An isoflavone compound or analogue thereof of the general formula II:



(II)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z_A is OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

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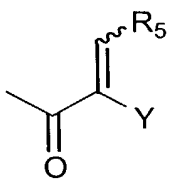
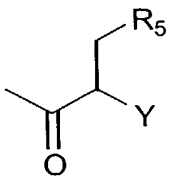
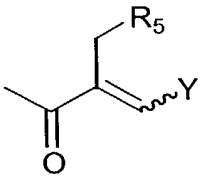
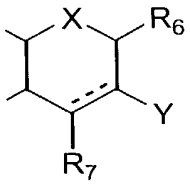
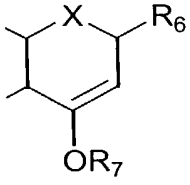
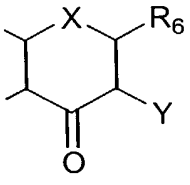
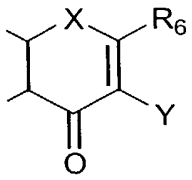
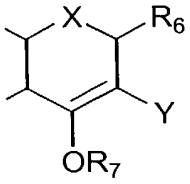
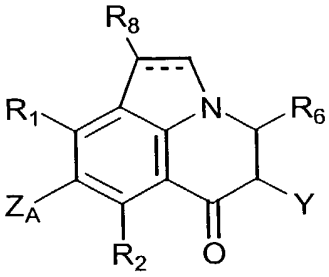
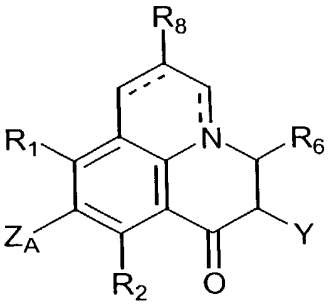
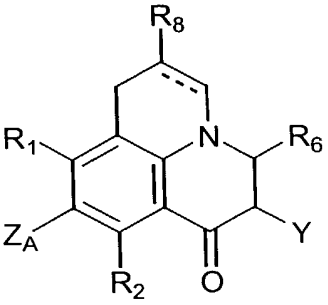



, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from






, or

W, A and B taken together with the groups to which they are associated comprise




, or

W and A taken together with the groups to which they are associated comprise

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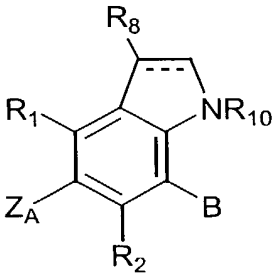
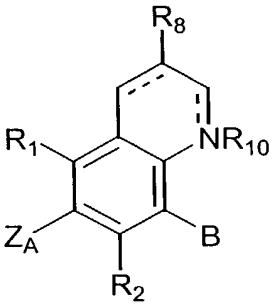
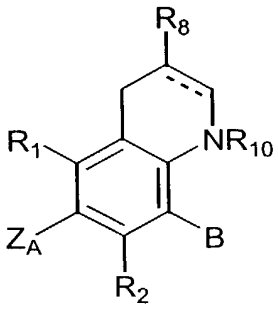
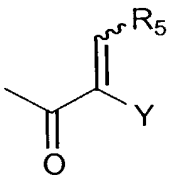
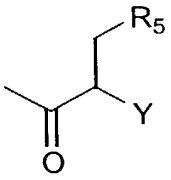
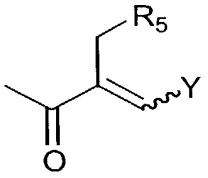




and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

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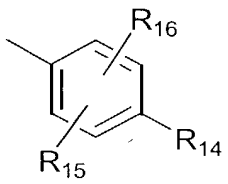
the symbol "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

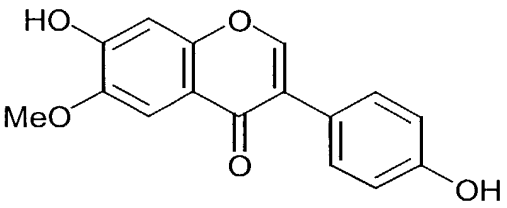
Y is

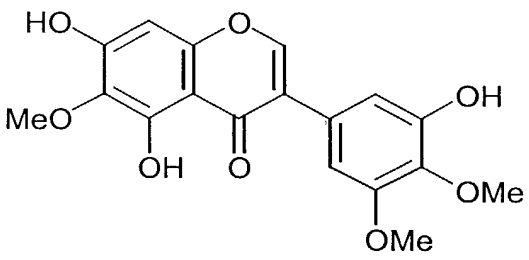


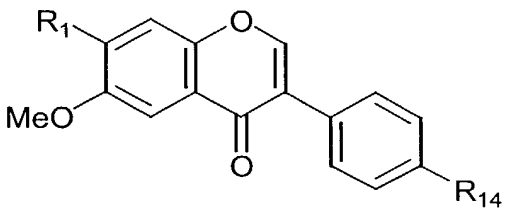
wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that the following compounds are excluded:







R_1 = OH, OMe
R_{14} = OH, OMe

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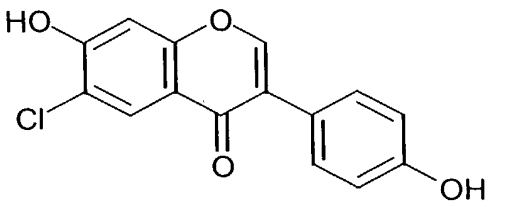
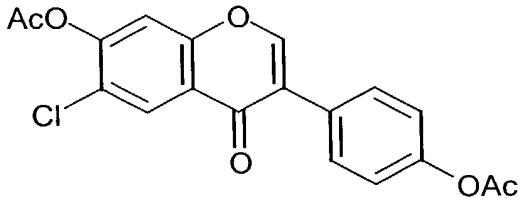
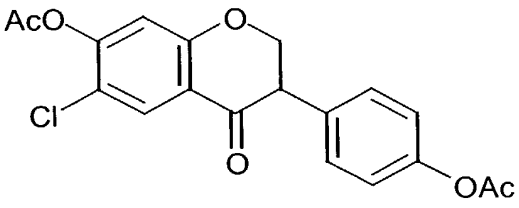
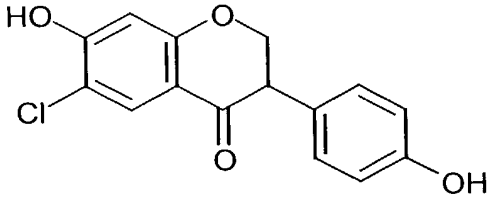
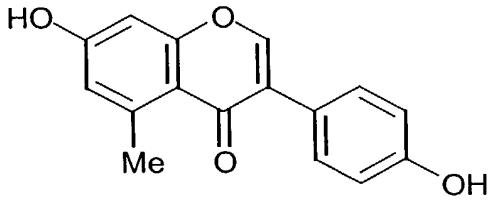
14. (New) A compound of formula I as defined in claim 12 or of formula II as defined in claim 13 selected from the group consisting of:

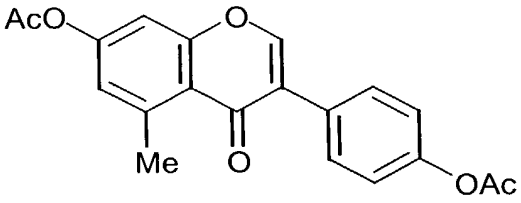


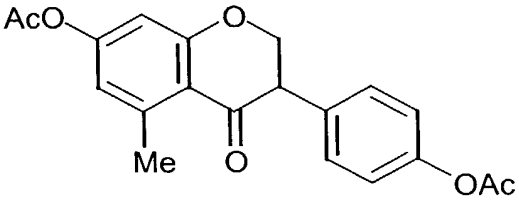


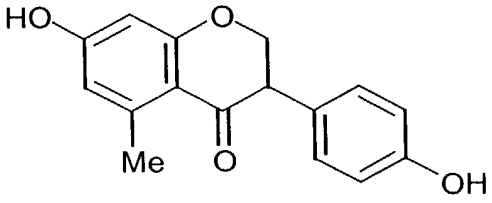












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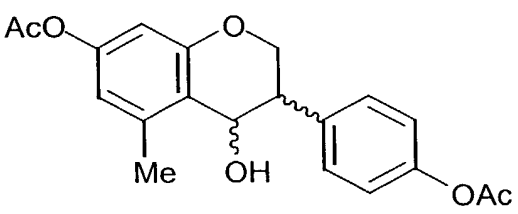

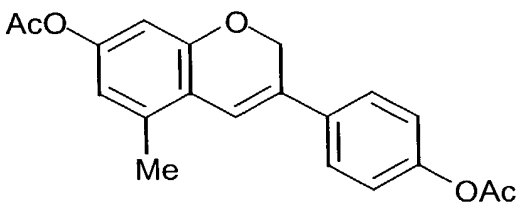

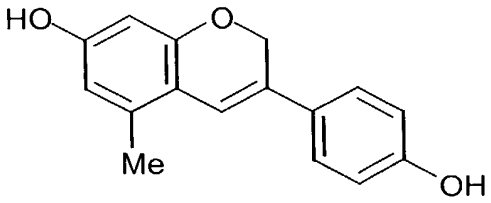

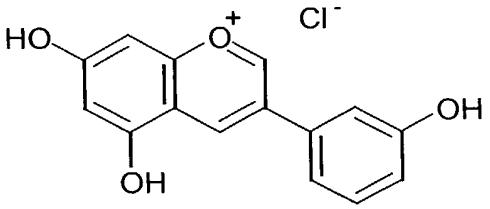

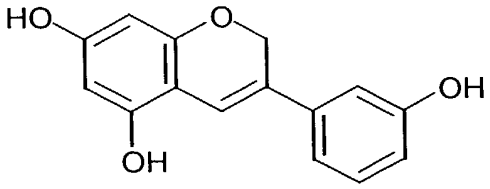

15. (New) A method for the treatment, prophylaxis, amelioration, defence against, or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buerger's Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimer's disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohn's disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds selected from formula

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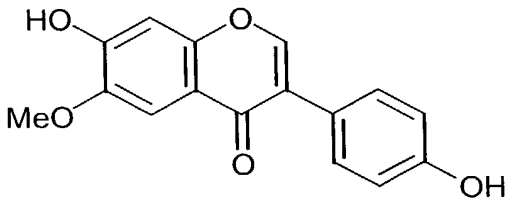
and formula II as defined in claim 12 or 13, respectively, with the proviso that the compound of formula



is specifically disclaimed for the treatment or prophylaxis of atherosclerosis.

16. (New) An agent according to claim 12 or 13 which comprises one or more compounds selected from formulae I and II as defined in claims 12 or 13 either alone or in association with one or more carriers and/or excipients.

17. (New) A therapeutic composition which comprises one or more compounds selected from formula I and II as defined in claims 12 or 13 in association with one or more pharmaceutical carriers and/or excipients.

18. (New) A drink or food-stuff, which contains one or more compounds selected from formulae I and II as defined in claims 12 or 13.

19. (New) A microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds selected from formulae I and II as defined in claims 12 or 13.

20. (New) One or more microorganisms which produce one or more compounds selected from formulae I and II as defined in claims 12 or 13.

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REMARKS

The examiner is respectfully requested to consider the above preliminary amendment prior to examination of the application. No new matter has been introduced by these amendments.

If there are any fees due in connection with the filing of this amendment, please charge the fees to Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 5, 2002

By: _____
Ernest F. Chapman
Reg. No. 25,961

EFC/FPD/peg

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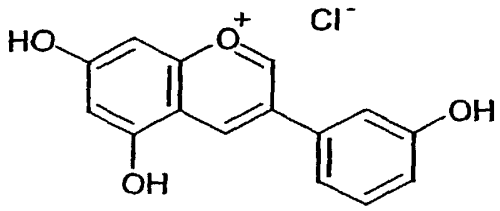
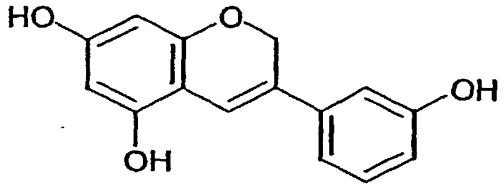
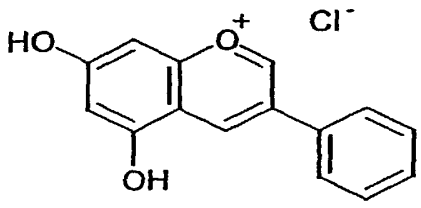
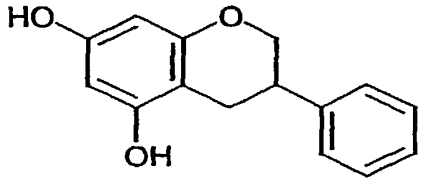
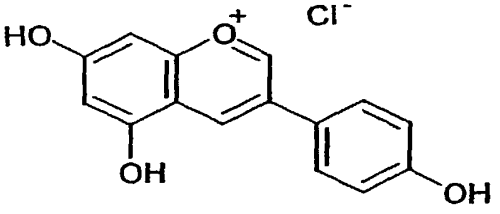
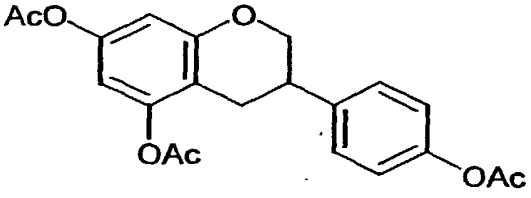


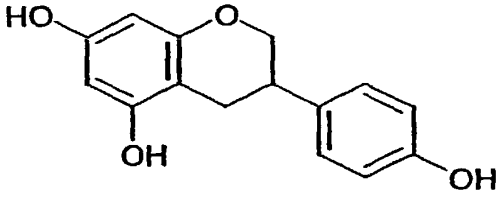












Compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

The amount of one or more compounds of formulae I and II which is required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient. Compounds of formulae I or II may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1299 (7th Edition, 1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in the range of 0.1 mg to 2 g; typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg.

The production of pharmaceutical compositions for the treatment of the therapeutic indications herein described are typically prepared by admixture of the compounds of the invention (for convenience hereafter referred to as the "active compounds") with one or more pharmaceutically or veterinarially acceptable carriers and/or excipients as are well known in the art.

The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or excipient may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose, for example, a tablet, which may contain from 0.5% to 59% by weight of the active compound, or up to 100% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, optical, buccal (for example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any

given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may

conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1% to 60% w/v of active compound and are administered at a rate of 0.1 ml/minute/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination of two or more thereof. The active compound is generally present at a concentration of from 0.1% to 0.5% w/w, for example, from 0.5% to 2% w/w. Examples of such compositions include cosmetic skin creams.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 M to 0.2 M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research 3* (6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 M to 0.2 M active ingredient.

The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices.

Compounds of the present invention have potent antioxidant activity and thus find wide application in pharmaceutical and veterinary uses, in cosmetics such as skin creams to prevent skin ageing, in sun screens, in foods, health drinks, shampoos, and the like.

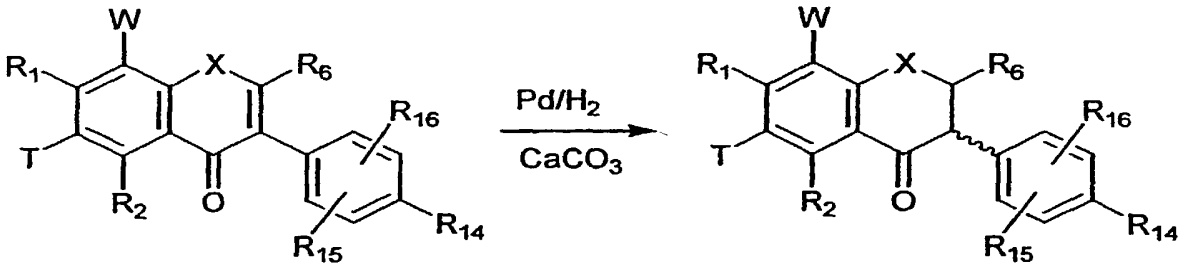
It has surprisingly been found that compounds of the formulae I or II interact synergistically with vitamin E to protect lipids, proteins and other biological molecules from oxidation.

Accordingly a further aspect of this invention provides a composition comprising one or more compounds of formulae I or II, vitamin E, and optionally a pharmaceutically, veterinarially or cosmetically acceptable carriers and/or excipients.

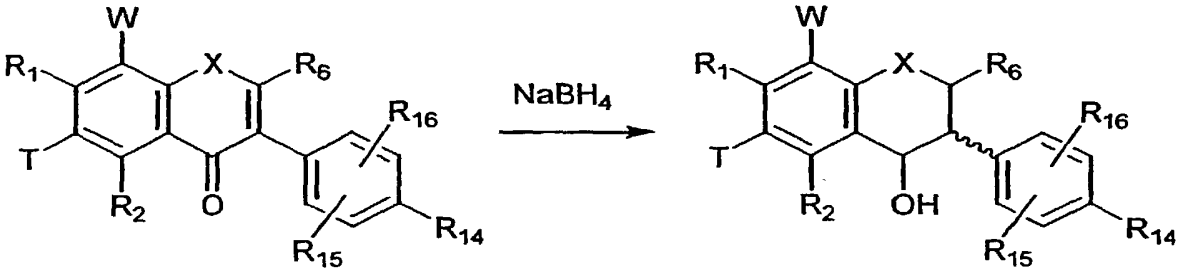
Therapeutic methods, uses and compositions may be for administration to humans or animals, such as companion and domestic animals (such as dogs and cats), birds (such as chickens, turkeys, ducks), livestock animals (such as cattle, sheep, pigs and goats) and the like.

Compounds of formulae I and II may be prepared by standard methods known to those skilled in the art. Suitable methods may be found in, for example, International Patent Application WO 98/08503 which is incorporated herein in its entirety by reference. Methods which may be employed by those skilled in the art of chemical synthesis for constructing the general ring structures depicted in formulae I and II are depicted in schemes 1-8 below. Chemical functional group protection, deprotection, synthons and

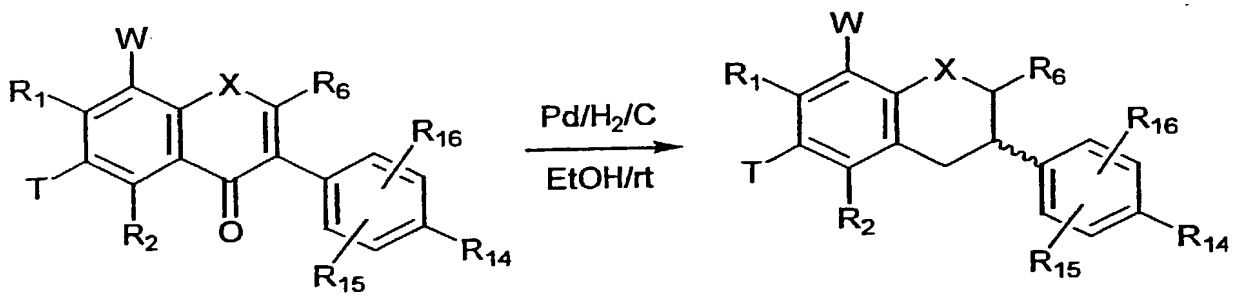
other techniques known to those skilled in the art may be used where appropriate in the synthesis of the compounds of the present invention. In the formulae depicted in the schemes below the moities R_1, R_2, R_6, R_8, R_{14}, R_{15}, R_{16}, W and X are as defined above. The moiety T is either Z or Z_A as defined in formulae I or II above. Reduction of the isoflavone derivatives may be effected by procedures well known to those skilled in the art including sodium borohydride reduction, and hydration over metal catalysts such as Pd/C, $Pd/CaCO_3$ and Platinum(IV)oxide (Adam's catalyst) in protic or aprotic solvents. The end products and isomeric ratios can be varied depending on the catalyst/solvent system chosen. The schemes depicted below are not to be considered limiting on the scope of the invention described herein.



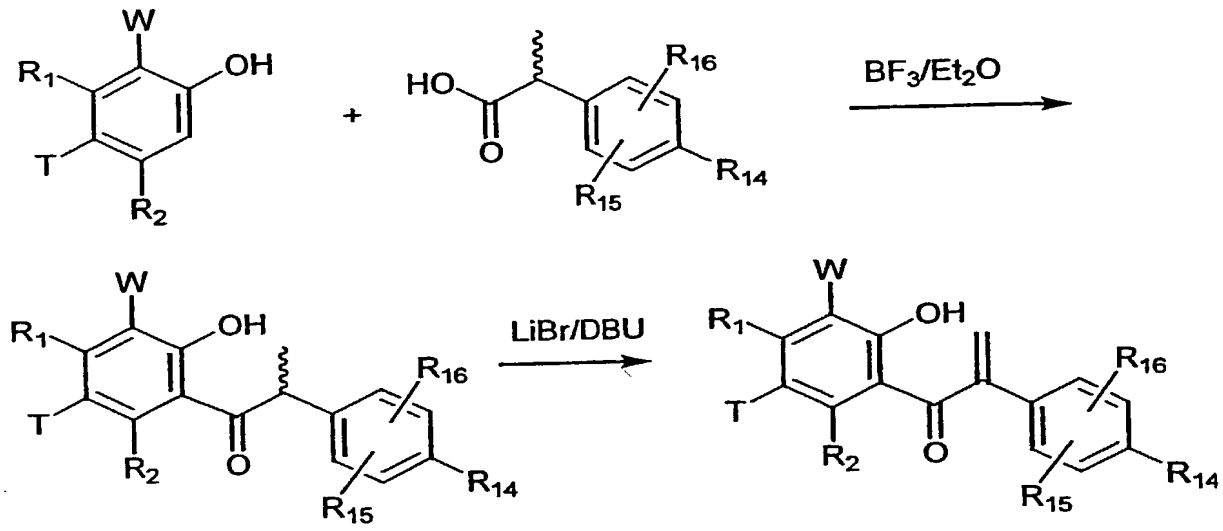
Scheme 1



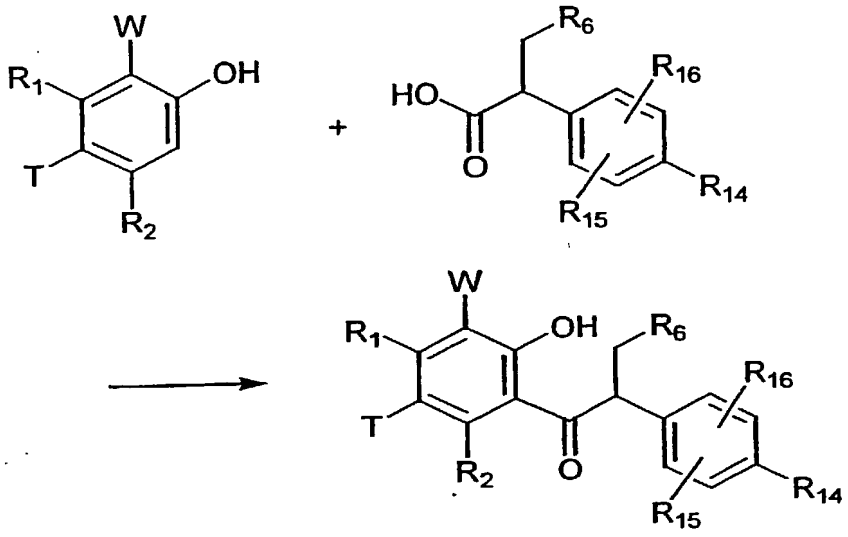
Scheme 2



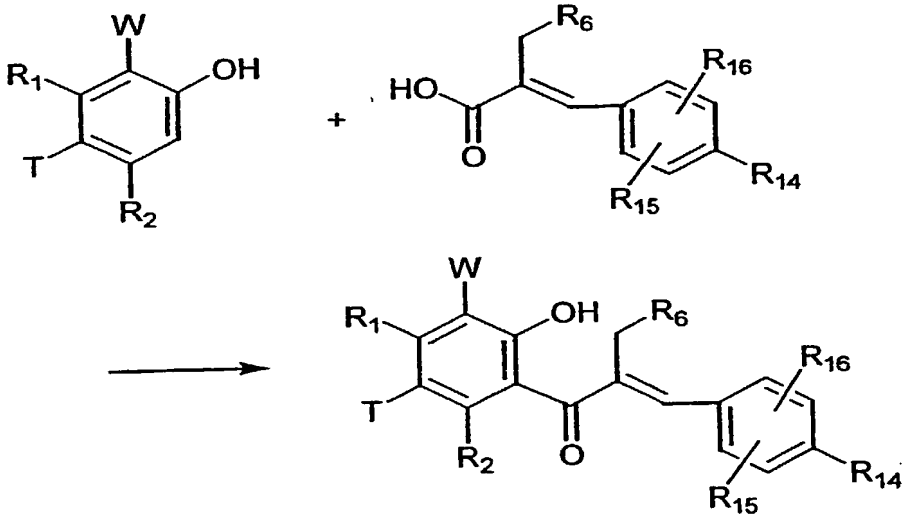
Scheme 3



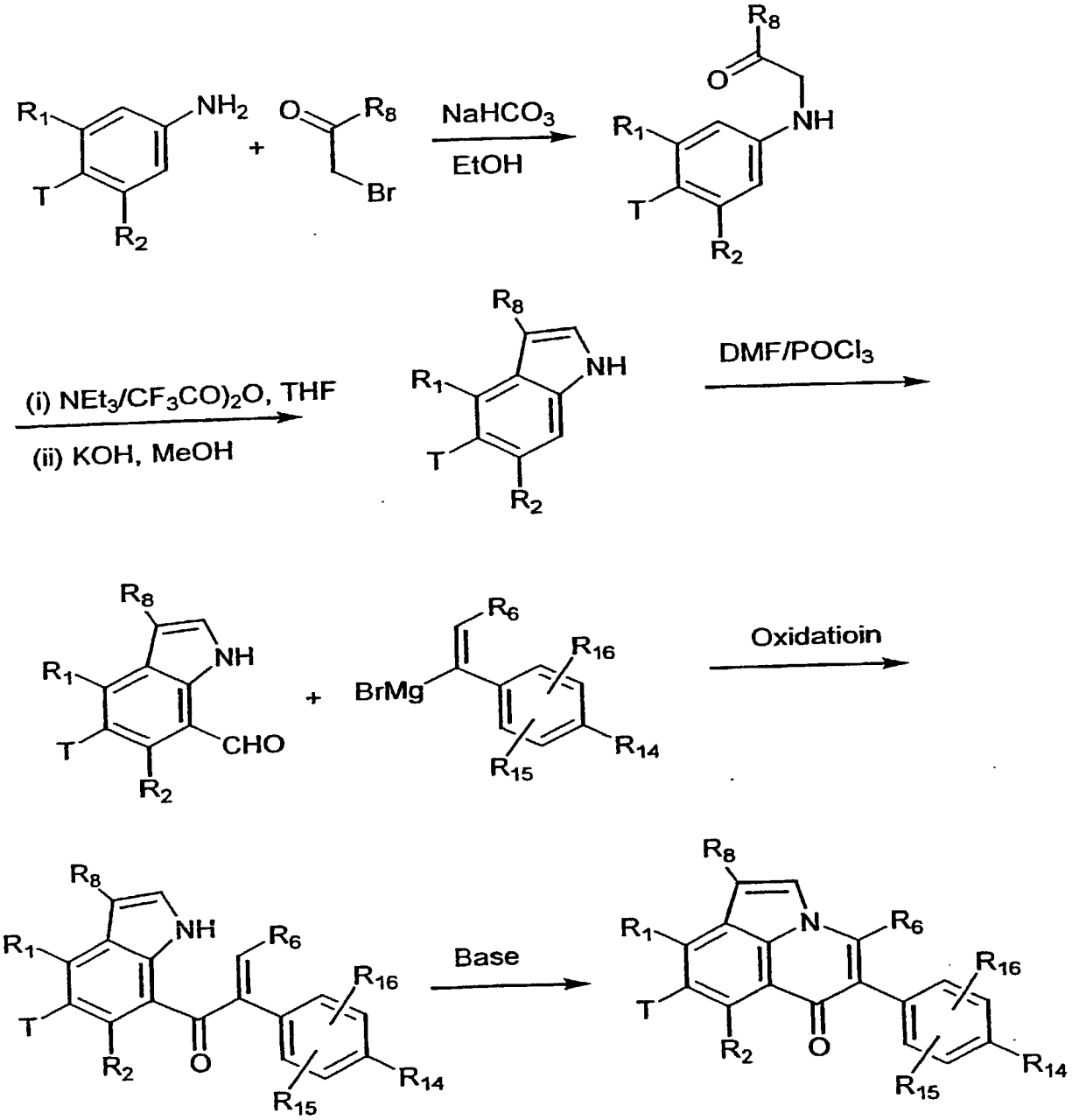
Scheme 4



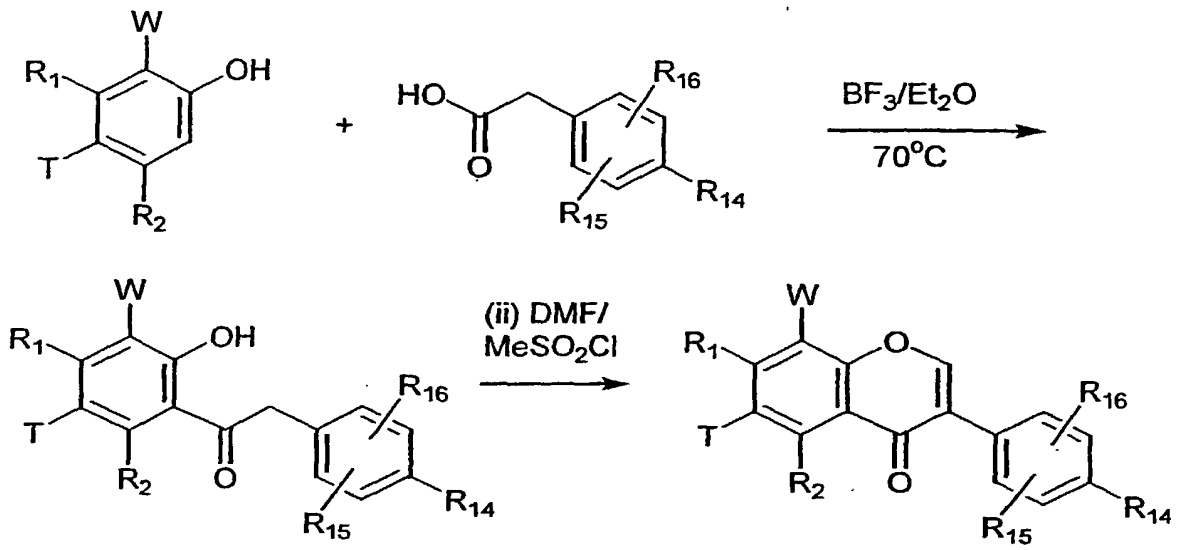
Scheme 5



Scheme 6


R1
NH2
T
R2
O
R8
Br
NaHCO3
EtOH
R8
O
NH
R1
T
R2
(i) NEt3/CF3CO)2O, THF
(ii) KOH, MeOH
R8
NH
R1
T
R2
DMF/POCl3
R8
NH
R1
T
CHO
R2
+
BrMg
R6
R16
R14
R15
Oxidatioin
R8
NH
R1
T
R2
O
R6
R16
R14
R15
Base
R8
N
R1
T
R2
O
R6
R16
R14
R15

Scheme 7



Scheme 8

EXAMPLE 1

General Syntheses of Substituted Isoflavones

6-Chloro-4',7-dihydroxyisoflavone was synthesised by the condensation of 4-chlororesorcinol with 4-hydroxyphenylacetic acid to afford 5-chloro-2,4,4'-trihydroxydeoxybenzoin. Cyclisation of the intermediate deoxybenzoin was achieved by treatment with dimethylformamide and methanesulfonyl chloride in the presence of boron triflouride etherate.

By varying the substitution pattern on the resorcinol or phenylacetic acid groups numerous other substituted isoflavones can also be synthesised in a similar manner. For example starting with 5-methyl resorcinol affords 4',7-dihydroxy-5-methylisoflavone, whilst use of 3-hydroxy phenyl acetic acid in the general synthetic method affords 3'-hydroxy isoflavone derivatives.

Isoflavan-4-ones

EXAMPLE 2

Synthesis of 6-Chloro-4',7-diacetoxyisoflavone

A mixture of 6-chloro-4',7-dihydroxyisoflavone (1.25 g, 4.3 mmol), acetic anhydride (7.5 ml) and pyridine (1.4 ml) was heated in an oil bath at 105-110° C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with aqueous methanol (50%) and dried to yield 6-chloro-4',7-diacetoxyisoflavone (1.2g, 75%) as colourless prisms. ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $OCOCH_3$), 2.41 (s, 3H, $OCOCH_3$), 7.16 (d, 2H, J 8.6 Hz, ArH), 7.36 (s, 1H, H8), 7.57 (d, 2H, J 8.6 Hz, ArH), 8.00 (s, 1H, H5). 8.37 (s, 1H, H2).

EXAMPLE 3

Synthesis of 6-Chloro-4',7-diacetoxyisoflavan-4-one

Adam's catalyst (0.045g) was added to a solution of 6-chloro-4',7-diacetoxyisoflavone (0.25g, 0.7 mmol) in ethyl acetate (30 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 6-chloro-4',7-diacetoxyisoflavan-4-one (0.15g, 60%) as colourless plates. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.37 (s, 3H, $OCOCH_3$), 3.98 (dd, 1H, J 6.0 Hz, 7.5 Hz, H3), 4.68 (m, 2H, H2), 6.87 (s, 1H, H8), 7.07 (d, 2H, J 8.6 Hz, ArH), 7.27 (d, 2H, J 8.6 Hz, ArH), 8.01 (s, 1H, H5).

EXAMPLE 4

Synthesis of 6-Chloro-4',7-dihydroxyisoflavan-4-one

Imidazole (0.60g) was added to a suspension of 6-chloro-4',7-diacetoxyisoflavan-4-one (0.24g, 0.06 mmol) in absolute ethanol (5.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 6-chloro-4',7-

dihydroxyisoflavan-4-one (0.14g, 75%) as a white powder. 1H NMR (d_6-acetone): δ 3.87 (t, 1H, J 7.2 Hz, H3), 4.64 (d, 2H, J 6.2 Hz, H2), 6.59 (s, 1H, H8), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.10 (d, 2H, J 8.7 Hz, ArH), 7.70 (bs, 1H, OH), 7.77 (s, 1H, H5).

EXAMPLE 5

Synthesis of 4',7-Diacetoxy-5-methylisoflavone

A mixture of 4',7-dihydroxy-5-methylisoflavone (1.51g, 5.6 mmol), acetic anhydride (9 ml) and pyridine (1.7 ml) was heated in an oil bath at 105-110°C for 1h. After cooling the mixture to room temperature, it was stirred for a further 30 min during which time the diacetate crystallised from the solution. The product was filtered, washed thoroughly with water and recrystallised from methanol to yield 4',7-diacetoxy-5-methylisoflavone as colourless prisms (1.8g, 91%). m.p. 195-97°C, ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $OCOCH_3$), 2.35 (s, 3H, $OCOCH_3$), 2.87 (s, 3H, Me), 6.92 (bs, 1H, H8), 7.12 (bs, 1H, H5), 7.16 (d, 2H, J 8.7 Hz, ArH), 7.55 (d, 2H, J 8.7 Hz, ArH), 7.89 (s, 1H, H2).

EXAMPLE 6

Synthesis of 4',7-Diacetoxy-5-methylisoflavan-4-one

Palladium on barium sulfate (5%, 0.06g) was added to a solution of 4',7-diacetoxy-5-methylisoflavone (0.30g, 0.8 mmol) in ethyl acetate (50 ml) and the mixture was stirred at room temperature under a hydrogen atmosphere for 24h. The catalyst was removed by filtration through Celite and the resulting filtrate was evaporated *in vacuo*. The residue was recrystallised from ethanol to yield 4',7-diacetoxy-5-methylisoflavan-4-one (0.20g, 67%) as colourless plates. m.p. 143-45°C, ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $OCOCH_3$), 2.30 (s, 3H, $OCOCH_3$), 2.62 (s, 3H, Me), 3.95 (t, 1H, J 7.2 Hz, H3), 4.62 (d, 2H, J 6.8 Hz, H2), 6.59 (d, 1H, J 2.2 Hz, H8), 6.66 (d, 1H, J 2.2 Hz, H5), 7.07 (d, 2H, J 8.3 Hz, ArH), 7.28 (d, 2H, J 8.3 Hz, ArH).

EXAMPLE 7

Synthesis of 4',7-Dihydroxy-5-methylisoflavanone

Imidazole (0.63g) was added to a suspension of 4',7-diacetoxy-5-methylisoflavan-4-one (0.50g, 1.4 mmol) in absolute ethanol (20.0 ml) and the mixture was refluxed for 45 min under argon. The solution was concentrated under reduced pressure and distilled water (10 ml) was added to the residue. The mixture was left overnight in the fridge and the resulting precipitate was filtered, washed with water and dried to yield 4',7-dihydroxy-5-methylisoflavan-4-one (0.25g, 66%) as a white powder. ^{1}H NMR (d_6-acetone): δ 2.51 (s, 3H, Me), 3.76 (t, 1H, J 5.7 Hz, H3), 4.57 (d, 2H, J 7.1 Hz, H2), 6.26 (d, 1H, J 2.2 Hz, H8), 6.35 (d, 1H, J 2.2 Hz, H5), 6.78 (d, 2H, J 8.7 Hz, ArH), 7.11 (d, 2H, J 8.7 Hz, ArH).

Isolflavan-4-ols and Isoflav-3-enes

EXAMPLE 8

Synthesis of 4'-7-Diacetoxy-5-methylisoflavan-4-ol

4'-7-Diacetoxy-5-methylisoflavan-4-ol was prepared by the reduction of 4'-7-diacetoxy-5-methylisoflavone (0.25g) with Adam's catalyst in ethyl acetate (30 ml) under a hydrogen atmosphere for 72 hours. The solution was filtered through a pad of Celite to yield predominantly *cis*-4'-7-diacetoxy-5-methylisoflavan-4-ol. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, $OCOCH_3$), 2.30 (s, 3H, $OCOCH_3$), 2.62 (s, 3H, Me), 3.24 (dt, 1H, J 3.4 Hz, J 11.8 Hz, H3), 4.31 (ddd, 1H, J 1.4 Hz, 3.6 Hz, 10.5 Hz, H2); 4.57 (dd, 1H, J 10.5 Hz, 11.8 Hz, H2), 4.82 (bs, 1H, H4), 6.51 (d, 1H, J 2.1 Hz, H8), 6.59 (d, 1H, J 2.1 Hz, H6), 7.06 (d, 2H, J 8.6 Hz, ArH), 7.29 (d, 2H, J 8.6 Hz ArH).

EXAMPLE 9

Synthesis of 4',7-Diacetoxy-5-methylisoflav-3-ene

4',7-Diacetoxy-5-methylisoflav-3-ene was prepared by the dehydration of cis- and trans-4'-7-diacetoxy-5-methylisoflavan-4-ol (0.2g) with phosphorus pentoxide (2.0g) in dry dichloromethane (20 ml). The crude product was chromatographed on silica column using dichloromethane as the eluent. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $OCOCH_3$), 2.31 (s, 3H,

$OCOCH_3$), 2.36 (s, 3H, Me), 5.08 (s, 2H, H2), 6.49 (d, 1H, J 2.0 Hz, H8), 6.52 (d, 1H, J 2.2 Hz, H5), 6.89 (s, 1H, H4), 7.14 (d, 2H, J 8.6 Hz, ArH), 7.44 (d, 2H, J 8.6 Hz, ArH).

EXAMPLE 10

Synthesis of 4',7-Dihydroxy-5-methylisoflav-3-ene

4',7-Dihydroxy-5-methylisoflav-3-ene was prepared from 4',7-diacetoxy-5-methylisoflav-3-ene by the removal of the acetoxy groups by hydrolysis under standard conditions.

EXAMPLE 11

Synthesis of 3',5,7-Trihydroxyisoflavylium chloride

Phosphoryl chloride (1.75 ml) was added to a mixture of the monoaldehyde (0,95g) and phloroglucinol dihydrate (1.6g) in acetonitrile (10 ml). The mixture was stirred at 30°C for 20 minutes and then at room temperature for 3 hours. The orange precipitate was filtered and washed with acetic acid to yield the isoflavylium salt.

EXAMPLE 12

Synthesis of Isoflav-3-ene-3',5,7-triol

Isoflav-3-ene-3',5,7-triol was prepared by the reduction of 3',5,7-trihydroxyisoflavylium chloride (0.5g) with sodium cyanoborohydride (0.33g) in ethyl acetate (11 ml) and acetic acid (3 ml) and chromatographic separation of the resulting mixture of isoflav-3-ene and isoflav-2-ene mixture. ^1H NMR (d_6-acetone): δ 4.99 (s, 2H, H2), 5.92 (d, 1H, J 2.0 Hz, ArH), 6.04 (d, 1H, J 2.2 Hz, ArH), 6.78-7.18 (m, 5H, ArH).

Isoflavans

EXAMPLE 13

Synthesis of Isoflavan-5,7-diol

Isoflavan-5,7-diol was prepared by the reduction of a suspension of 5,7-dihydroxyisoflavylium chloride (0.5g) with Palladium-on-charcoal (5%, 0.1g) in acetic acid (15 ml) containing ethyl acetate (2.5 ml) under a hydrogen atmosphere. The crude

product was recrystallised from 1,2-dichloromethane to give the isoflavan as colourless needles, m.p. 76-78°C (lit m.p. 77-79°C).

EXAMPLE 14

Synthesis of 4',5,7-Triacetoxyisoflavan

4',5,7-Triacetoxyisoflavan was prepared by the reduction of a suspension of 4',5,7-trihydroxyisoflavylium chloride (0.31g) with platinum oxide (0.04g) in a mixture of acetic anhydride (2.0 ml) and ethyl acetate (10 ml) under a hydrogen atmosphere. After the removal of catalyst the crude product was refluxed with pyridine (0.5 ml) and the resulting triacetate was isolated by evaporation of the solvent and crystallisation of the residue. M.p. 126-28°C.

EXAMPLE 15

Synthesis of Isoflavan-4',5,7-triol

Isoflavan-4',5,7-triol was prepared from 4',5,7-triacetoxyisoflavan by the removal of the acetyl groups by hydrolysis. M.p. 206-8°C.

EXAMPLE 16

The binding affinity of various compounds of the invention for both subtypes of the estrogen receptor was determined with the "Estrogen Receptor Alpha or Beta Competitor Assay Core HTS Kit" supplied by Panvera Corporation (Product No. P2614/2615). 6-Chloro-4',7-dihydroxyisoflavan-4-one showed good competitive binding to the estrogen receptor with the following results:

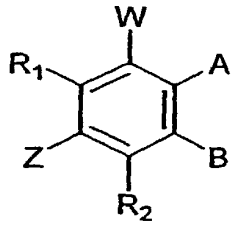
ER alpha receptor = 37.82 uM
ER beta receptor = 32.14 uM

The results show that the compounds of the present invention have particular application in the treatment of diseases associated with or resulting from estrogenic effects, androgenic effects, vasodilatory and spasmodic effects, inflammatory effects and oxidative effects.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The inventions also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The claims defining the invention are as follows:

1. An isoflavone compound or analogue thereof of the general formula I:



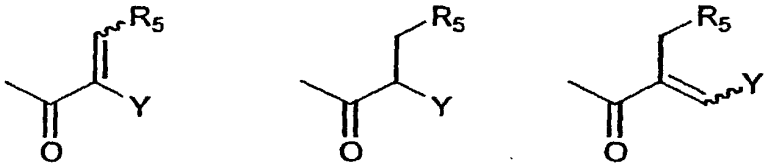
(I)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

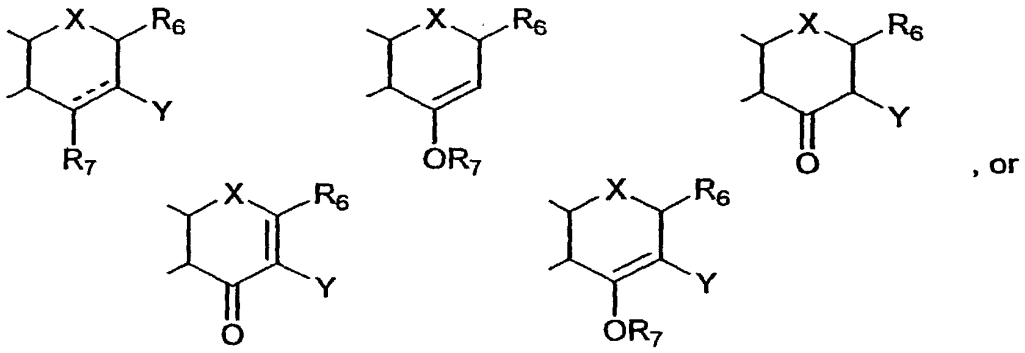
Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



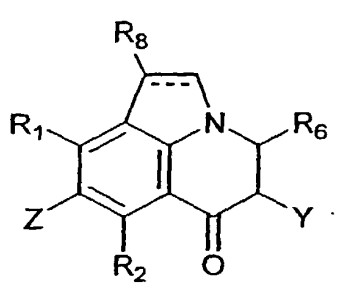
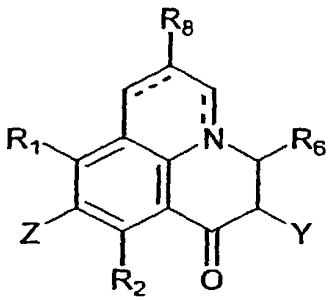
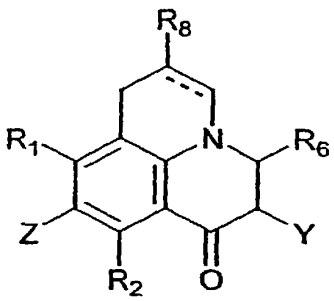
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

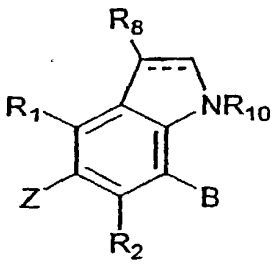
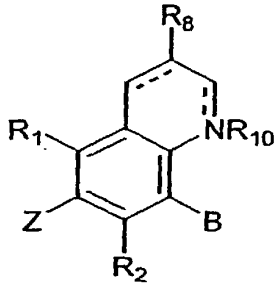
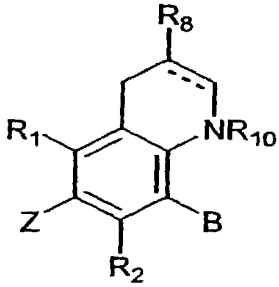


, or

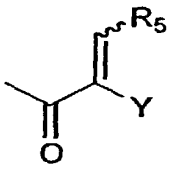
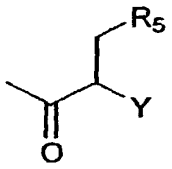
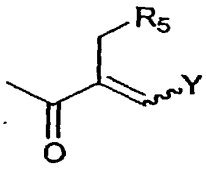
W, A and B taken together with the groups to which they are associated comprise




, or

W and A taken together with the groups to which they are associated comprise

and B is

wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

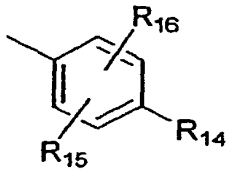
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

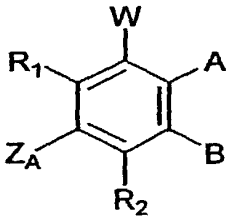
R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

2. An isoflavone compound or analogue thereof of the general formula II:



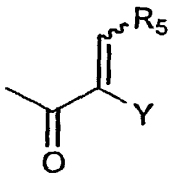
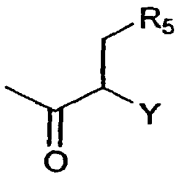
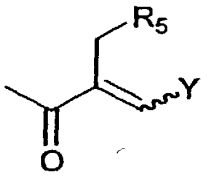
(II)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

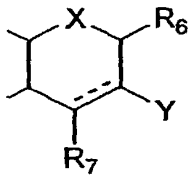
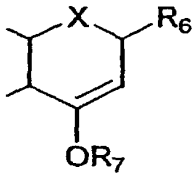
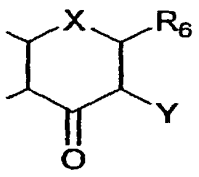
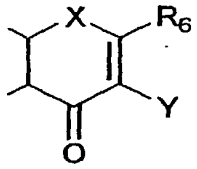
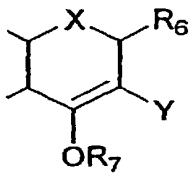
Z_A is OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

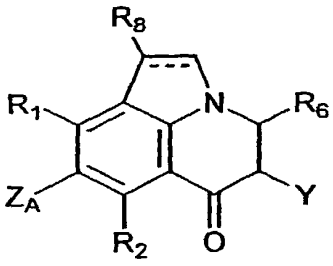
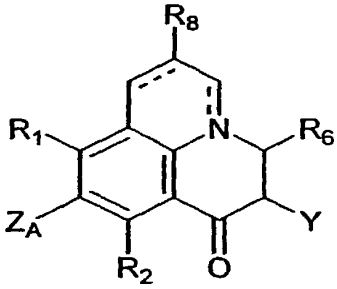
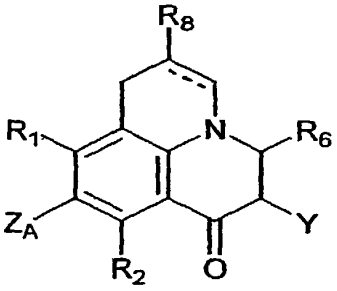
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from

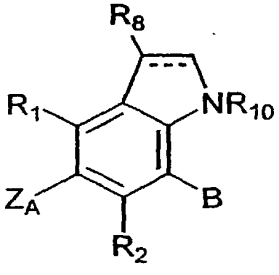
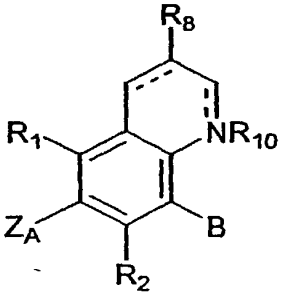
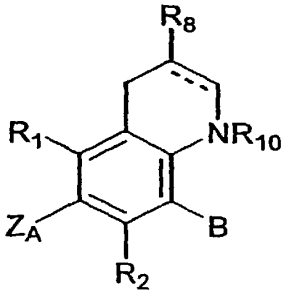
, or

W, A and B taken together with the groups to which they are associated comprise

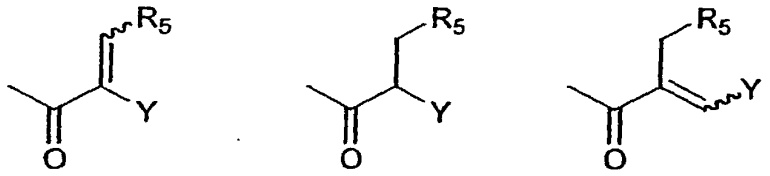




, or

W and A taken together with the groups to which they are associated comprise

and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

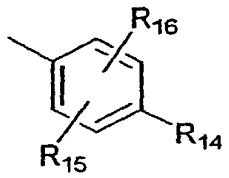
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

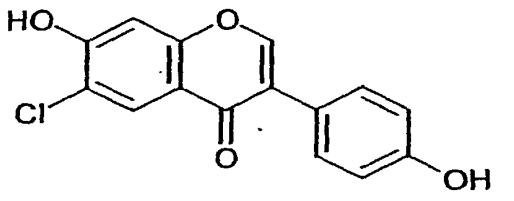
Y is

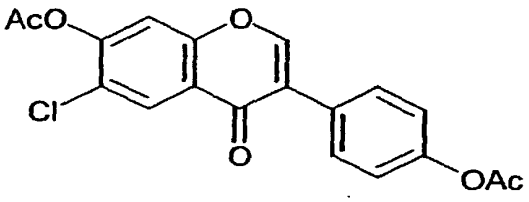


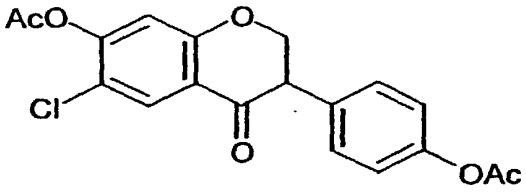
wherein

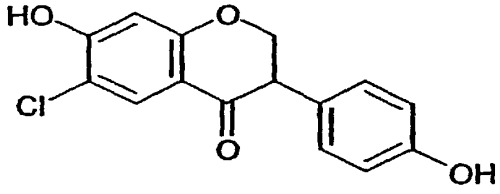
R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

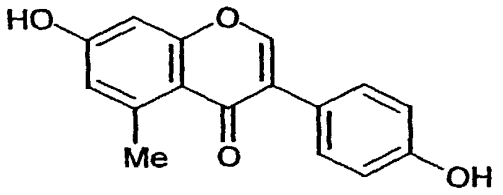
3. A compound of formulae I as defined in claim 1 or of formula II as defined in claim 2 selected from the group consisting of:

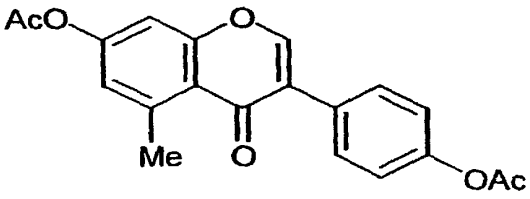


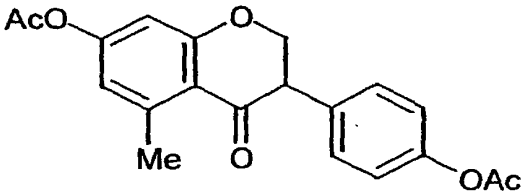


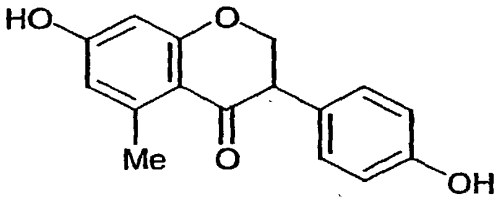


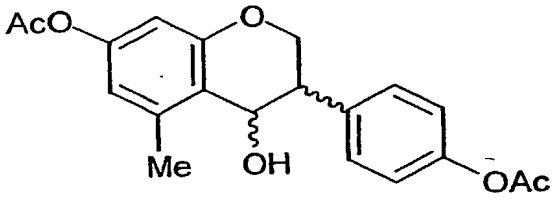


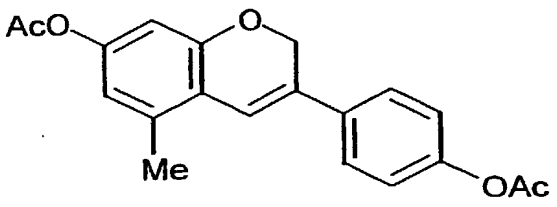









AcO
O
Me
OH
OAc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O
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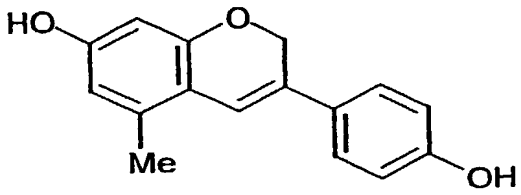
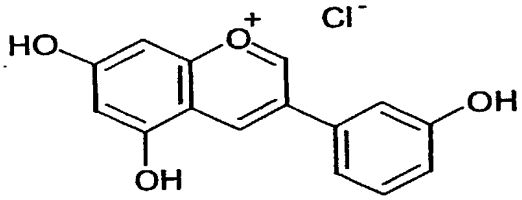
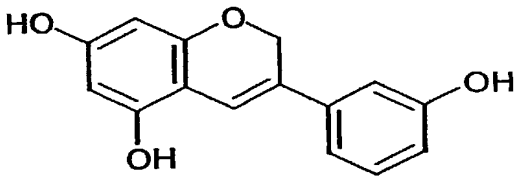

HO
O
Me
OH


HO
O+
Cl-
OH
OH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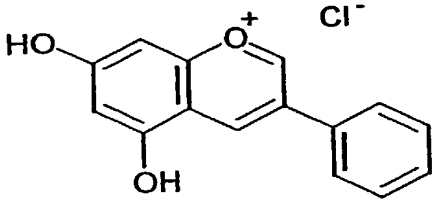
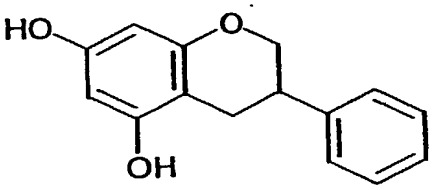
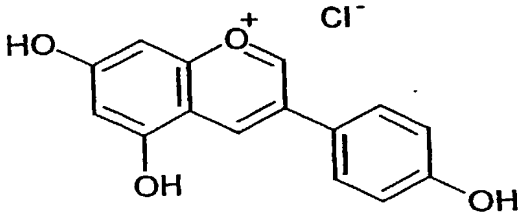
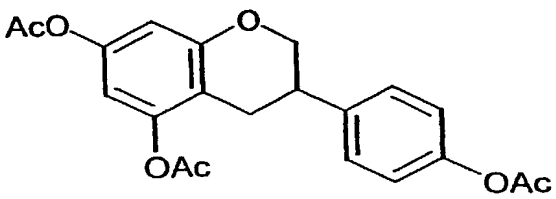
O
OH
OH


HO
O+
Cl-
OH


HO
O
OH


HO
O+
Cl-
OH
OH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O
OAc
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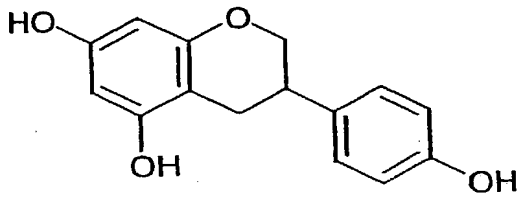
HO
O
OH
OH

4. A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds selected from formulae I and II.

5. Use of one or more compounds selected from formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

6. Use of one or more compounds selected from formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more therapeutic indications according to claim 4.

7. An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications according to claim 4 which comprises one or more compounds selected from formulae I and II either alone or in association with one or more carriers or excipients.

8. A therapeutic composition which comprises one or more compounds selected from formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

9. A drink or food-stuff, which contains one or more compounds selected from formulae I and II.

10. A microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds selected from formulae I and II.

11. One or more microorganisms which produce one or more compounds selected from formulae I and II.

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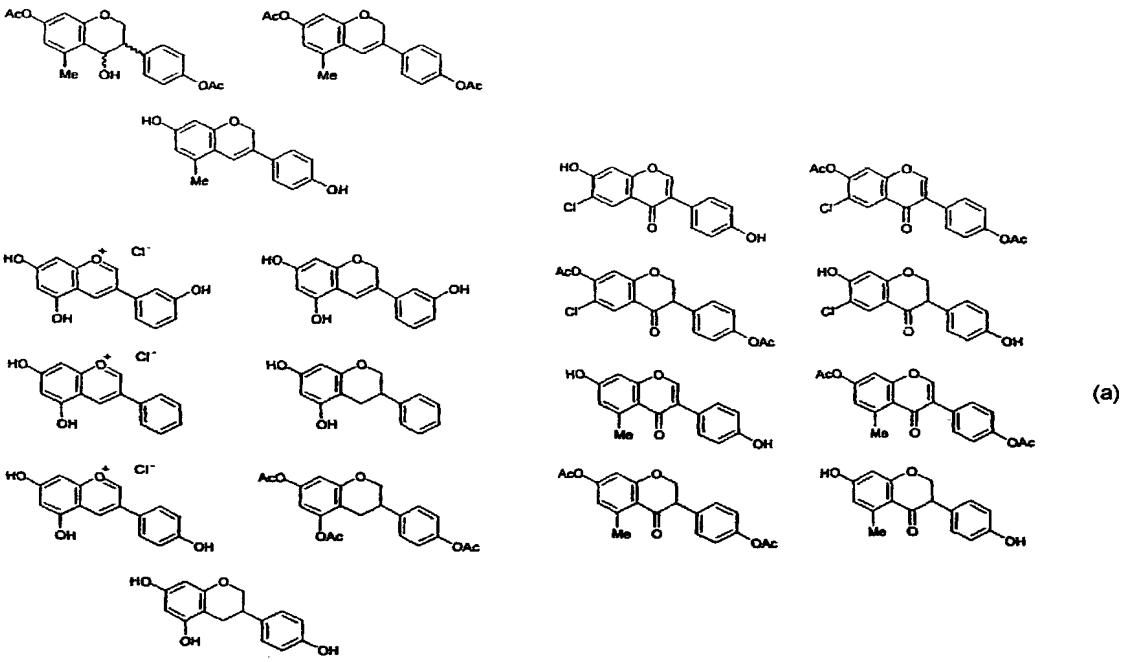
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF



(a)

(57) Abstract: Isoflavone compounds are described and recommended as therapeutic agents. Exemplified and preferred compounds are (a). Indications show compounds have good competitive binding to estrogen receptors. This is exemplified.

WO 01/17986 A1

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

the specification of which
☐ is attached and/or
☒ was filed on March 5, 2002, as United States Application Serial No. and was amended on March 5, 2002,
☒ PCT International Application No. PCT/AU00/01056,filed September 6, 2000.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
Australia	PQ 2661	September 6, 1999	☒ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., CUSTOMER NUMBER 22,852** Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432;

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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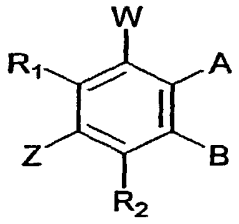
COMPOSITIONS AND THERAPEUTIC METHODS INVOLVING ISOFLAVONES AND ANALOGUES THEREOF

This invention relates to compounds, formulations, drinks, foodstuffs, methods and therapeutic uses involving, containing, comprising, including and/or for preparing certain isoflavone compounds and analogues thereof.

According to an aspect of this invention there is provided isoflavone compounds and analogues thereof of the general formula I:



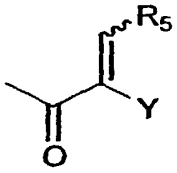
(I)

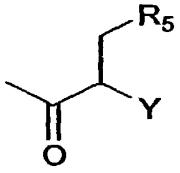
in which

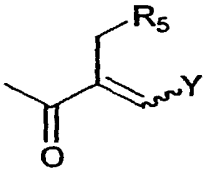
R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

Z is hydrogen, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from

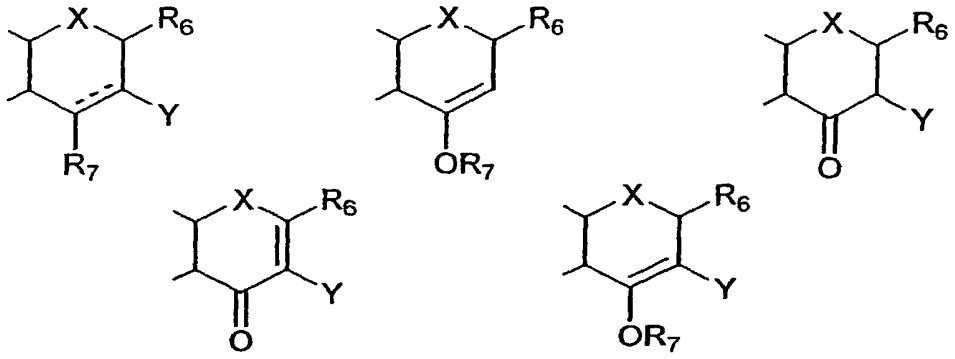






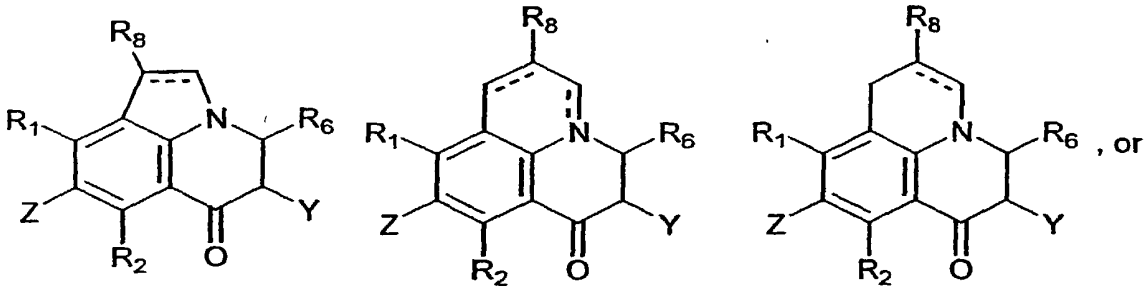
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



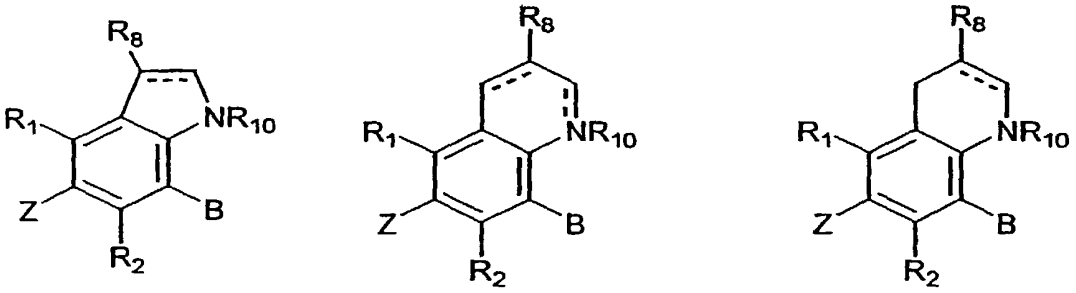
, or

W, A and B taken together with the groups to which they are associated comprise

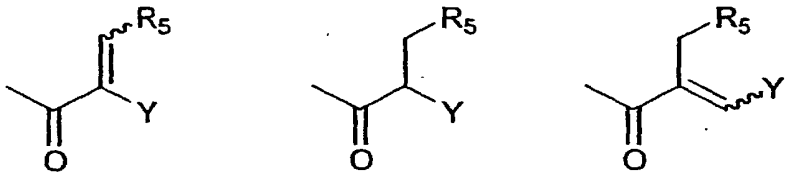


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen to which they are attached comprise pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

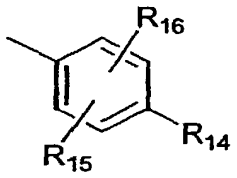
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

Y is



wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

with the proviso that

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

W is hydrogen, then

Y is not 4-hydroxyphenyl or 4-alkylphenyl;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, then

W is not hydrogen;

when

R_1 is hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_2 is not hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined; and

when

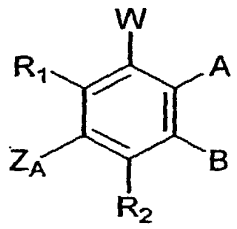
R_2 is hydrogen, hydroxy, OR_B where R_B is an amino acid or $C(O)R_A$ where R_A is as previously defined, and

Y is 4-hydroxyphenyl or 4-alkylphenyl, and

W is hydrogen, then

R_1 is not hydroxy, or $OC(O)R_A$ where R_A is alkyl or an amino acid.

According to another aspect of this invention there is provided isoflavone compounds and analogues thereof of the general formula II:



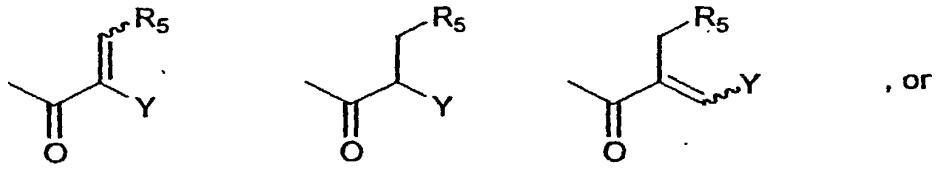
(II)

in which

R_1 and R_2 are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo,

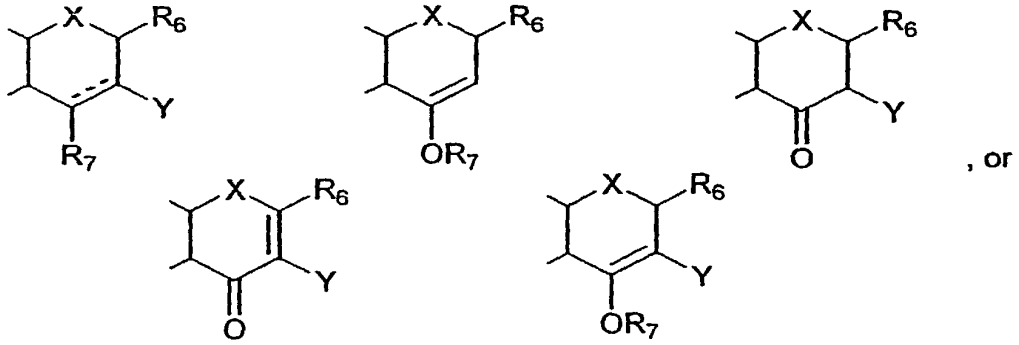
Z_A is OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, and

W is R_1, A is hydrogen, hydroxy, NR_3R_4 or thio, and B is selected from



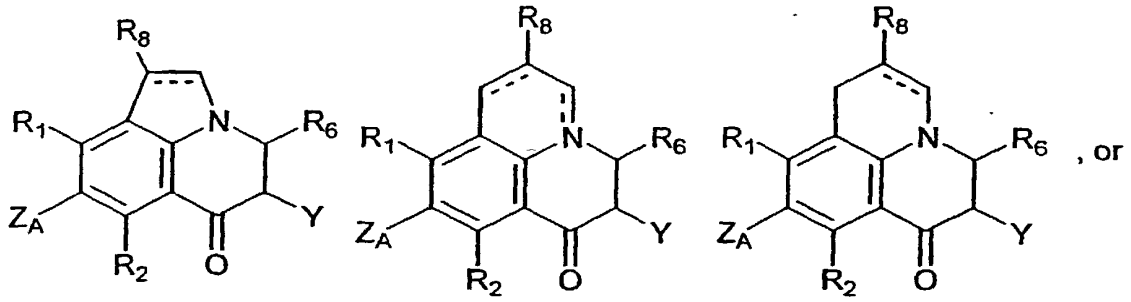
, or

W is R_1, and A and B taken together with the carbon atoms to which they are attached form a six-membered ring selected from



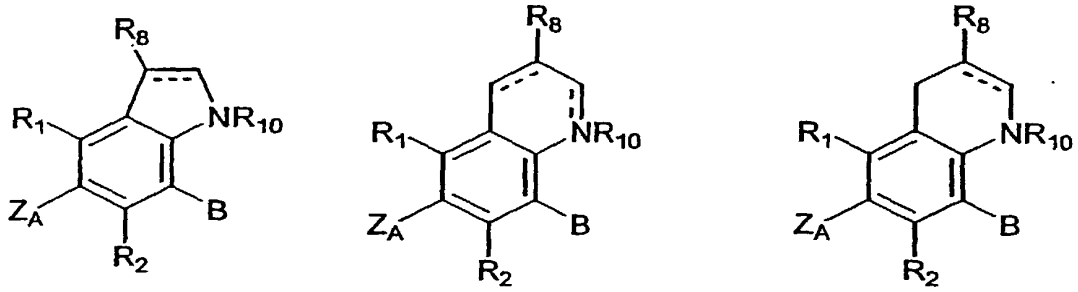
, or

W, A and B taken together with the groups to which they are associated comprise

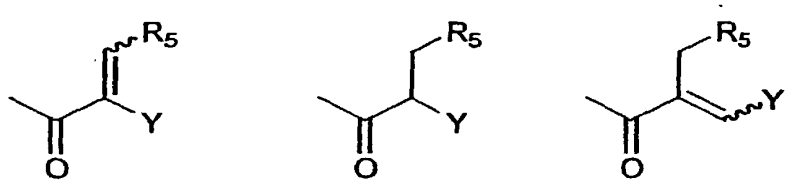


, or

W and A taken together with the groups to which they are associated comprise



and B is



wherein

R_3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, $C(O)R_{11}$ where R_{11} is hydrogen alkyl, aryl, arylalkyl or an amino acid, or CO_2R_{12} where R_{12} is hydrogen, alkyl, haloalkyl, aryl or arylalkyl,

R_4 is hydrogen, alkyl or aryl,

or R_3 and R_4 taken together with the nitrogen which they are attached are pyrrolidinyl or piperidinyl,

R_5 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, or CO_2R_{12} where R_{12} is as previously defined,

R_6 is hydrogen, hydroxy, alkyl, aryl, amino, thio, NR_3R_4, COR_{11} where R_{11} is as previously defined, CO_2R_{12} where R_{12} is as previously defined or $CONR_3R_4$,

R_7 is hydrogen, $C(O)R_{11}$ where R_{11} is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or $Si(R_{13})_3$ where each R_{13} is independently hydrogen, alkyl or aryl,

R_8 is hydrogen, hydroxy, alkoxy or alkyl,

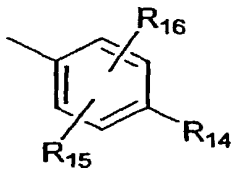
R_9 is alkyl, haloalkyl, aryl, arylalkyl, $C(O)R_{11}$ where R_{11} is as previously defined, or $Si(R_{13})_3$ where R_{13} is as previously defined,

R_{10} is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or dialkylamino,

the drawing "---" represents either a single bond or a double bond,

X is O, NR_4 or S, and

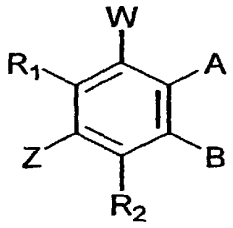
Y is



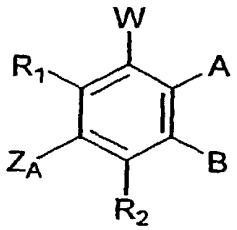
wherein

R_{14}, R_{15} and R_{16} are independently hydrogen, hydroxy, OR_9, $OC(O)R_{10}$, $OS(O)R_{10}$, CHO, $C(O)R_{10}$, COOH, CO_2R_{10}, $CONR_3R_4$, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo.

It has surprisingly been found by the inventors that compounds of the general formulae I and II:



(I)



(II)

in which

R_1, R_2, W, A, B, Z and Z_A are as defined above have particular utility and effectiveness in the treatment, prophylaxis, amelioration defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; atherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts.

Thus according to another aspect of the present invention there is provided a method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of menopausal syndrome including hot flushes, anxiety, depression, mood swings, night sweats, headaches, and urinary incontinence; osteoporosis; premenstrual syndrome, including fluid retention, cyclical mastalgia, and dysmenorrhoea; Reynaud's Syndrome; Reynaud's Phenomenon; Buergers Disease; coronary artery spasm; migraine headaches; hypertension; benign prostatic hypertrophy; all forms of cancer including breast cancer; uterine cancer; ovarian cancer; testicular cancer; large bowel cancer; endometrial cancer; prostatic cancer; uterine cancer; artherosclerosis; Alzheimers disease; inflammatory diseases including inflammatory bowel disease, ulcerative colitis, Crohns disease; rheumatic diseases including rheumatoid arthritis; acne; baldness including male pattern

baldness (alopecia hereditaria); psoriasis; diseases associated with oxidant stress including cancer; myocardial infarction; stroke; arthritis; sunlight induced skin damage or cataracts (for convenience hereafter referred to as the "therapeutic indications") which comprises administering to a subject a therapeutically effective amount of one or more compounds of formulae I and II as defined above.

Yet another aspect of the present invention is the use of compounds of formulae I and II for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

Still another aspect of the present invention is the use of one or more compounds of formulae I and II in the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications.

And another aspect of the present invention comprises an agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of the therapeutic indications which comprises one or more compounds of formulae I and II either alone or in association with one or more carriers or excipients.

A further aspect of the invention is a therapeutic composition which comprises one or more compounds of formulae I and II in association with one or more pharmaceutical carriers and/or excipients.

A still further aspect of the present invention is a drink or food-stuff, which contains one or more compounds of formulae I and II.

Another aspect of the present invention is a microbial culture or a food-stuff containing one or more microbial strains which microorganisms produce one or more compounds of formulae I and II.

Still another aspect of the present invention relates to one or more microorganisms which produce one or more compounds of formulae I and II. Preferably the microorganism is a purified culture, which may be admixed and/or administered with one or more other cultures which product compounds of formulae I and II.

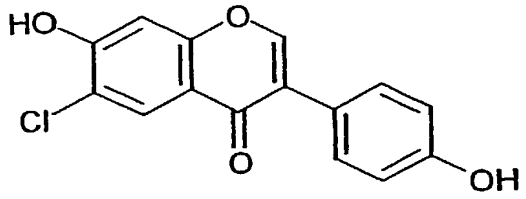
Throughout this specification and the claims which follow, unless the text requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The term "alkyl" is taken to mean both straight chain and branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, and the like. The alkyl group has 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably methyl, ethyl propyl or isopropyl. The alkyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino-carbonyl, di-(C_1-C_4-alkyl)-amino-carbonyl, hydroxyl, C_1-C_4-alkoxy, formyloxy, C_1-C_4-alkyl-carbonyloxy, C_1-C_4-alkylthio, C_3-C_6-cycloalkyl or phenyl.

The term "aryl" is taken to include phenyl and naphthyl and may be optionally substituted by one or more C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, carbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylcarbonyloxy or halo.

The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl.

Particularly preferred compounds of the present invention are selected from: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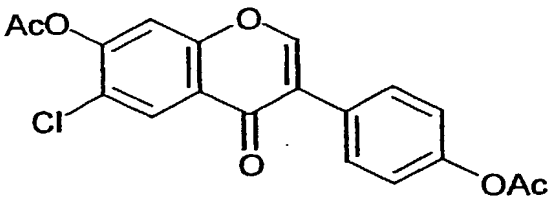
Cl
O
OH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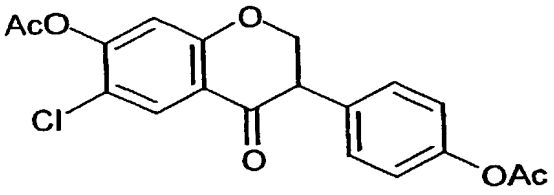
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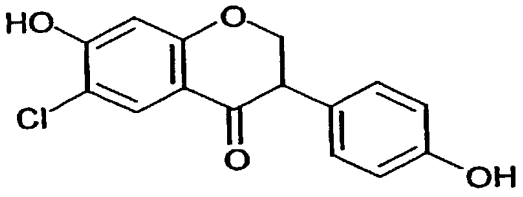
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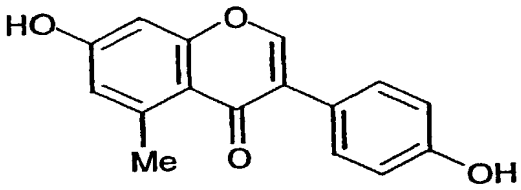
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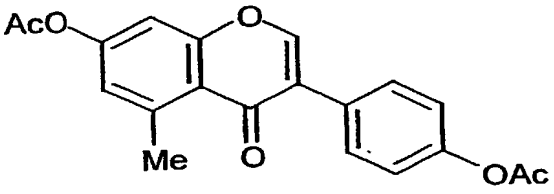
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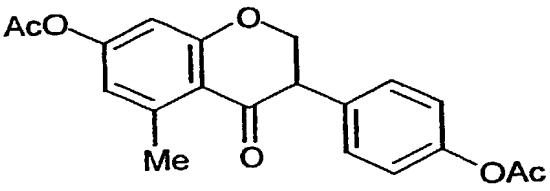
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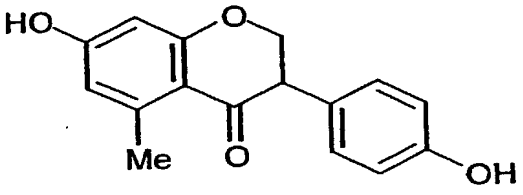
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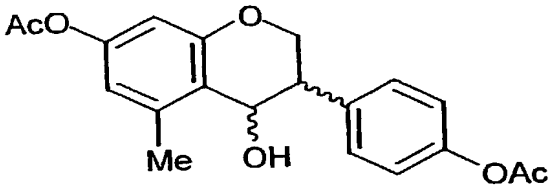
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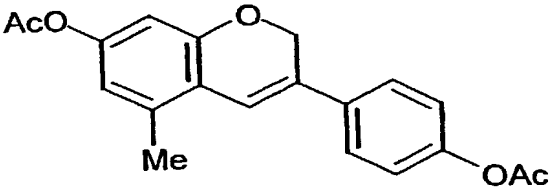
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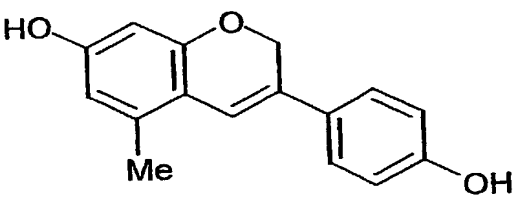
HO
O
Me
OH